Critical response to post-outbreak vaccination against foot-and-mouth disease

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Abstract. The effectiveness of vaccinations initiated after the onset of an infectious epidemic (post-outbreak vaccinations or POV) was retrospectively explored by modeling: 1) the days required by the infective agent to reproduce (replication cycle or RC), 2) the time required by the susceptible population to become protected after POV 3) the number, time and location of cases, 4) the Euclidean distance between the spatial units of analysis, and 5) the spatial environment where the epidemic occurred. The spatial epidemic model is composed of differential equations and used geo-coded data (Euclidean distances between county centroids). The epidemic transmission was assumed to be influenced by the inter-county (Euclidean) distance.

We used geo-temporal data on Foot-and-Mouth Disease (FMD) dispersion, based on the 2001 FMD epidemic that occurred in Uruguay, to evaluate: 1) vaccine potency, and 2) the time when a POV begins. Two vaccine types ("regular" and "high-potency", assumed to induce protective antibody titers within 7.1 or 3 days, repectively) and 4 POV starting times (5, 8, 12 and 15 post-outbreak days).

Findings support the hypothesis that the time available to achieve effective POV against FMD is brief. Reductions in epidemic size were marginal when POV began at or after the third RC. Because, in this scenario, the earliest time protective antibody levels could be achieved was either 8 days (high-potency vaccine) or 12 days post-outbreak (regular vaccine), the earliest time average susceptible farms may become protected is the end of the third (or fourth) RC, time at which a 3-digit epidemic size is likely to occur in FMD epidemics. Because this analysis assumed optimal conditions unlikely to be observed in all epidemics, the actual critical time to implement succesful POV may be shorter. This approach has the potential of being used to assess POV's cost-benefit ratios.

1. Introduction

Identification of the critical time available to choose and implement control measures, once an epidemic outbreak occurs, is a classic epidemiological problem [**36**]. Scientifically plausible and logistically feasible guidelines need to be based on historical data embedded within context-specific scenarios. Because the geographical features impact the spread of an epidemic, geo-temporal data of actual

1991 *Mathematics Subject Classification.* Primary 92D25, 92D30; Secondary 92B05, 92B15.

Key words and phrases. Foot-and-mouth Disease; spatial epidemic model; vaccination; reproductive number; differential equations.

epidemics that occurred in the past are needed to validate the guidelines. Although these data cannot prove any hypothesis, retrospective analysis of geo-temporal epidemic data can facilitate improving the estimate of the initial time window to start vaccinating.

Epidemic dispersal of rapidly disseminating infectious diseases is influenced by local factors, which tend to be discontinuous. For instance, farm, animal and road densities are distributed over space following non-normal/non-random distributions [**38**] and can facilitate (or hinder) epidemic dispersal in magnitudes and relationships rarely known before an epidemic breaks out.

Geographic Information Systems (GIS) facilitates the analysis of geo-temporal epidemic data on real time. Integrating these data with biological concepts (such as the time required by the infecting agent to reproduce or replication cycle) can help develop analytical methods to give real time estimates for the costs and benefits of alternative control policies [**37, 38**].

In previous work, the 2001 Foot-and-Mouth Disease (FMD) epidemic was modeled to estimate relevant parameters that assessed the effects of interventions [**11**]. Epidemic dispersal was modeled to depend on the distance between counties (proxy variable for connectivity) with transmission rates decaying exponentially fast with inter-county (Euclidean) distance. That model considered that interventions (i.e., animal movement ban) resulted in decreases in the average transmission rate. That study also modeled the mass vaccination program via two parameters: the rate at which farms were vaccinated and the rate at which vaccinated farms reached protective antibody levels. Chowell et al. [**11**] showed that a non-spatial model (based on the homogeneous mixing assumption) was not able to capture the initial take-off of the epidemic whereas the spatial model with inter-county (Euclidean) distance dependent transmission rate (as defined in Methods) gave a significantly better fit to the cumulative number of cases (outbreaks). However, that study did not explore the (sensitivity) impact of timely implementation of a mass vaccination campaign, and of the benefits of using a high potency vaccine.

Determining the time within which post-outbreak vaccinations (POV) should occur in order to become successful is a question of major epidemiological relevance. We use the spatial model, calibrated using data from the 2001 Uruguayan FMD epidemic [**11**] to evaluate the effects of POV on the final epidemic size. This information could help policy makers by guiding studies where the costs of emergency vaccinations are compared to measurable benefits (i.e., a reduction in total epidemic size). In our study, we considered a 30% reduction in epidemic size attributed to emergency vaccinations as a minimal measure of acceptable benefit. We assess two types of vaccines: a "regular" and a "high-potency" vaccine (assumed to induce protective antibody titers within 7.1 or 3 days, respectively), and 4 post-outbreak vaccination (POV) starting times (5, 8, 12 and 15 post-outbreak days or pod), interventions investigated in the context of the 2001 Uruguayan FMD epidemic.

The replication cycle of the FMD virus (FMDV) is approximately 3 days long [**1**]. High-potency vaccines against FMD induce protective titers of antibodies within approximately 3 days [**14**]. This disease did not exist in Uruguay in the previous decade and the index case was reported at farm level (i.e., early on in the epidemic progression). The scenario provided an opportunity to observe this epidemic over time and space and generate data that was used to evaluate the analytical model here described.

Our study focused on determining the time available to implement post-outbreak vaccinations that result in significant reductions of epidemic size (i.e., $\geq 30\%$) and estimating how effective the use of vaccines of different potency could lengthen this time.

2. Brief overview of FMD

FMD is a highly infectious illness of livestock with potential devastating consequences. The etiological agents of FMD is an aphthovirus that affects cloven-hoofed animals such as pigs, cattle, and sheep. Infected animals shed large amounts of the virus through the mouth and nose [**44**]. The virus can survive in objects such as shoes, clothes, or vehicle tires. The wind can carry the virus long distances [**22, 44**]. Recurrent FMD outbreaks have occurred in several regions of the world. In South America, FMD was first recorded in Argentina, Uruguay, and Brazil around 1870 as a result of the introduction of cattle from Europe during the early colonization days [**40**]. South America has reported recurring outbreaks of FMD, albeit the number of clinical FMD cases in that region has decreased considerably since the signing of the Hemispheric Plan for the Eradication of Foot-and-Mouth Disease (PHEFA) in 1987 [**13**].

The transmission dynamics of FMD involve immunological, epidemiological, geographical, and sociological factors. The average incubation period for FMD has been reported to be 3-6 days with a maximum of 14 days [**24, 25, 42**]. Latent animals progress to an infectious state that lasts for about 8 days. They are typically asymptomatic during the first 5 days of the infectious period [**29**] and then asymptomatic and infectious [**50**]. Hence, there is a small window ($3 - 5$ days) to detect and remove or isolate the infected animals from the rest. Animals that recover do so but with reduced weight and a diminished productivity [**19**] .

The transmission dynamics of FMD is tied in to geographical and sociological factors that are difficult to separate and/or quantify. FMD transmission between adjacent farms has been documented [**29, 19, 28**]. Long distance transmission through routes that include daily milk collection routes, cattle transportation, animal movement, or cattle relocation, etc. are not only possible but extremely likely [**41, 4**].

No models that include explicit transmission mechanisms (cause and effect), that is, deterministic models, have been able to incorporate all possible transmission routes effectively. The agent-based model known as EpiSims [**17**] provides an example of the cost and magnitude of validating a detailed model and has increased our understanding of the limitations of simple models [**9**]. Simple deterministic models can often yield useful insights, generate intriguing hypotheses, and guide future research [**3, 7**] and their analyses can be used to roughly evaluate the validity of control and intervention measures. Models that incorporate the immunological, epidemiological, sociological, and geographical dependent factors for FMD would be extremely complex. Their validation would require knowledge of a large number of parameters, their distributions, and large amounts of data. The information required would include knowledge of the rates of movements of key individuals, human and animal traffic between farms, lags in reporting, impact of holidays, highly heterogeneous contact structures (between susceptible hosts, "vectors", and infected hosts), geography as well as immunological (variability in susceptibility)

and epidemiological factors. Prior work [**36, 37**] provides rough quantitative estimates of the importance of geographical factors on the rate of FMD spread. It was shown that intervention response times depended strongly on the spatial (regions) distribution of farms.

The cost of FMD epidemics can be high. More than four million animals were destroyed during the 2001 FMD epidemic in Great Britain [**16**] and the exportation of animal goods was cancelled for roughly a year. During the 2001 FMD epidemic in Great Britain, two teams of researchers developed highly refined models to aid in the decision-making process [**29, 19**] and concluded that massive culling was the best strategy to control the ongoing FMD epidemic. Their conclusions relied on models that incorporated data on the location of farms, farm animal density, and measures of animal heterogeneity within farms. Longitudinal data on the number of farms infected and the culling process were available [**16**]. On the other hand, during the 2001 FMD epidemic in Uruguay, movement restrictions and a mass vaccination campaign were put in place. The estimated cost of controlling the Uruguayan epidemic was 13.6 million US$ of which 7.5 million were spent on vaccine purchase [**44**].

3. Materials and Methods

An explicit discrete spatial deterministic model that incorporates specific interventions is introduced (Figure 1a). The epidemiological unit is the farm. Farms are classified as susceptible (S), latent (L), infectious and undetected (I), and detected and isolated (J). Farms are aggregated at the level of counties. A susceptible farm in county i that is in contact with the virus enters the latent (uninfectious and asymptomatic) class (L) at the rate $\sum_{j=1}^{n} \beta_{ij} I_j$. In other words, the rate of infection is assumed to be proportional to the sum of the weighted prevalences of infected farms from all counties j. The inter-patch connectivity matrix β_{ij} measure the impact on county i from direct and indirect "contacts" between $i-$county and the $j-$county. These "contacts" may be the result of animal relocation or movement, from the sharing of milk routes (drivers as "mechanical" vectors or carriers), shared veterinarians or overlapping visitors (buyers, salesmen of farm products, etc. [**44, 41**]). It is assumed that latently infected farms "progress" towards the infectious class after a mean time of $1/k$ days and that infectious farms are detected and isolated from other farms at the per-capita rate $\alpha(t)$. That is, $\alpha(t)$ is the average time required to detect and isolate an infected farm.

Matrix β_{ij} will depend on different factors including the spatial "closeness" of counties and the traffic between counties in terms of animal movement, truck movement, milk collection, human movement, etc. However, data on the traffic/flow among counties was not available. Hence, we recurred to inter-county (Euclidean) distance between counties as a proxy variable.

Inter-county (Euclidean) distance dependent transmission rate. Far away farms are assumed to be less likely to share the same veterinarians or milk trucks or visitors. Having no reliable information on the county specific frequency of movement of potential "carriers." It is assumed that the rate of transmission β_{ij} between farms in counties i and j decays exponentially fast with the Euclidean distance of

their respective county centroids. The elements of the "mixing" or "contact" matrix β_{ij} [**3**] are therefore expressed as

$$\beta_{ij} = \beta(t)\ e^{-qd_{i,j}}, \tag{3.1}$$

where $\beta(t)$ denotes the average transmission rate of infectious farms within each county at time t, d_{ij} is the distance between the centroids of counties i and j (Figure 2), and the parameter q (1/km) which quantifies the extent of average local spread ($1/q$ can also be interpreted as the FMD mean transmission range). Small values of q lead to widespread influence, whereas large values of q support the hypothesis that local spread is the key. For simplicity, uniform mixing within each county is assumed, that is, $d_{ii} = 0$.

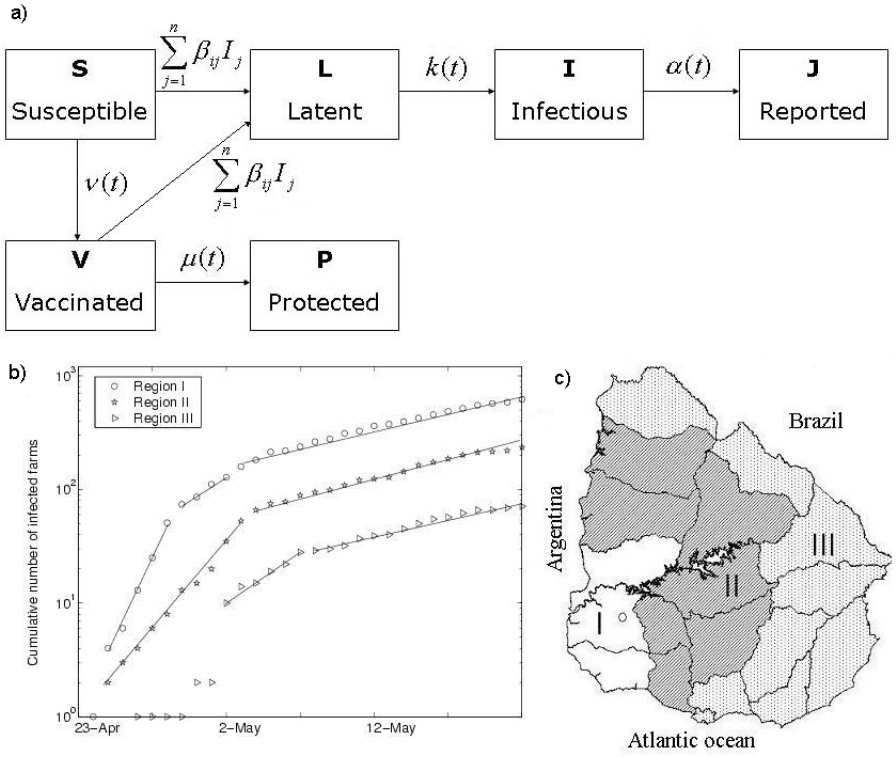

FIGURE 1. (a) Schematic representation of the status progression for farms in a given county used to model the epidemic, as explained in the text. (b) The initial growth rate for Region I, II and III. (c) Region I, II and III comprise 3, 7 and 8 Uruguayan states, respectively. The circle (Region I) denotes the site where the index case was reported.

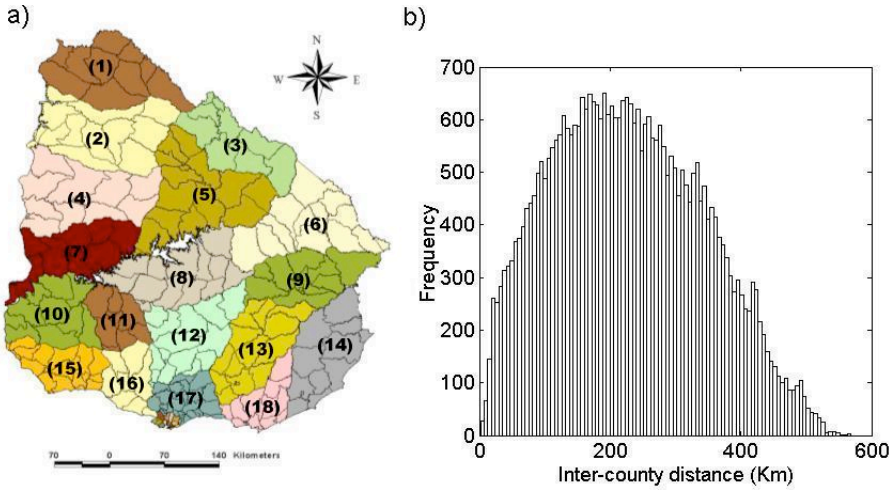

FIGURE 2. (a) Map of Uruguay with department (in color: 1) Artigas, 2) Salto, 3) Rivera, 4) Paysandu, 5) Tacuarembo, 6) Cerro Largo, 7) Rio Negro, 8) Durazno, 9) Treinta y Tres, 10) Soriano, 11) Flores, 12) Florida, 13) Lavalleja, 14) Rocha, 15) Colonia, 16) San Jose, 17) Canelones, 18) Maldonado) and county divisions and (b) distribution of intercounty (Euclidean) distances which were obtained using a geographic information system (GIS). The centroid of each county was used to compute euclidean distances.

The model with movement restrictions (time-dependent transmission rate $\beta(t)$) and mass vaccination is the following (see compartment diagram in Figure 1a) :

$$
\left\{
\begin{array}{rcl}
\dot{S}_i &=& -S_i(t)\sum_{j=1}^{n}\beta_{ij}(t)I_j(t) - \nu(t)S_i(t) \\
\dot{V}_i &=& \nu(t)S_i(t) - V_i(t)\sum_{j=1}^{n}\beta_{ij}(t)I_j(t) - \mu(t)V_i(t) \\
\dot{L}_i &=& (S_i(t)+V_i(t))\sum_{j=1}^{n}\beta_{ij}(t)I_j(t) - k(t)L_i(t) \\
\dot{I}_i &=& k(t)L_i(t) - \alpha(t)I_i(t) \\
\dot{J}_i &=& \alpha(t)I_i(t) \\
\dot{P}_i &=& \mu(t)V_i(t)
\end{array}
\right. \tag{3.2}
$$

The dot denotes time derivatives while S_i, L_i, I_i, and J_i denote the number of susceptible, latent, infectious, and removed/isolated farms in county i ($i = 1, 2, ..., n$). The distribution of the number of farms per county is given in ref. [**11**]. The above system falls within the class of metapopulation models that have been used extensively to study ecological processes in heterogeneous patchy environments. In fact, the spatially dependent transmission rates $\{\beta_{ij}\}$ correspond to the metapopulation patch connectivity index [**23**] once we re-interpret d_{ij} as a measure of the influence of the landscape on migration. The elements of $\{d_{ij}\}$ here are set of as "indices" that capture the effects of local transmission factors such as wind direction and animal heterogeneity within farms (dairy, beef, etc.). Here, the county connectivity d_{ij} is approximated by the distance between counties. Susceptible farms in county i (S_i) are vaccinated at rate ν (V_i); vaccinated farms in V_i enter the protected class P_i at rate μ; vaccinated farms in county i that have not yet reached protective

levels (class P) enter the latent (uninfectious and asymptomatic) class (L) at the rate $\sum_{j=1}^{n} \beta_{ij} I_j$. The total cumulative number of reported infected farms as a function of time is given by $C(t) = \sum_{i=1}^{n} J_i(t)$ while the daily number of new reported infected farms is given by $\dot{C}(t)$, that is by $\alpha(t) \sum_{i=1}^{n} I_i(t)$.

The dependence of parameters $\beta(t)$, $\alpha(t)$, $\nu(t)$, and $\mu(t)$ on time allow for the possibility of implementing control measures at different times [**10**]. For simplicity, these parameters are modelled as simple step functions

$$\beta(t) = \begin{cases} \beta_0 & t < \tau_m \\ \beta & t \geq \tau_m \end{cases} \tag{3.3}$$

$$\alpha(t) = \begin{cases} \alpha_0 & t < \tau_v \\ \alpha & t \geq \tau_v \end{cases} \tag{3.4}$$

$$\nu(t) = \begin{cases} 0 & t < \tau_v \\ \nu & t \geq \tau_v \end{cases} \tag{3.5}$$

$$\mu(t) = \begin{cases} 0 & t < \tau_v \\ \mu & t \geq \tau_v \end{cases} \tag{3.6}$$

where $\tau_m = 5$ is the epidemic day when movement restrictions were put in place and $\tau_v = 13$ is the time when mass vaccination started.

3.1. Model implementation. The 19 Uruguayan states are grouped into three contiguous regions (Regions I, II and III) (Figure 1b,c). They experienced significantly different prevalences [**36**]. Most cases accumulated in Region I where the epidemic started [**18**]. Fewer cases occurred in the surrounding Region II, and the least number of cases were reported in Region III [**36**]. Figure 2b shows the distribution of all the intercounty distances. Using geo-referenced outbreak reports obtained from public records of the Uruguayan Ministry of Livestock, Agriculture, and Fisheries (MGAP) [**32**], the Pan-american Health Organization [**35**], and the World Organization for Animal Health (OIE) [**49**] were used to construct a table of the number of daily new reported infected farms during the first 79 days of the epidemic (Figure 3). Each infected farm was associated geographically with a region, state, and county. The focus of the epidemic was in Region I where the epidemic started (1003 infected farms (57%)). This region includes the states of Soriano, with 463 outbreaks (26%); Colonia, with 362 (21%); and Rio Negro, with 178 (10%).

3.2. Parameter estimation and model selection. The model parameters $\mathbf{\Theta} = (\beta(t), k(t), \alpha(t), q(t), \nu(t), \mu(t))$ and the initial number of exposed and infectious farms ($E(0)$ and $I(0)$) were estimated from the cumulative number of reported farms (t_i, y_i), where t_i denotes the i^{th} reporting time (79 reporting days) and y_i is the cumulative number of reported farms by least-squares fitting to $C(t, \mathbf{\Theta})$ (the cumulative number of reported farms for our ODE model with interventions (3.2)) in Region I (where the outbreak started and the majority of outbreaks occurred)

[**11**]. This gives a system of 5 (equations per county) * 42 (counties in Region I) = 210 differential equations. MATLAB (The MathWorks, Inc.) was used to carry out the least-squares fitting procedure. Initial conditions were chosen within the appropriate ranges ($0 < \beta < 100$, $1/5 < k < 1/3$, $1/12 < \alpha < 1/4$, $0 < q < 10$, $0 < \nu < 10$, $0 < \mu < 10$). Parameter optimization was carried out using the Levenberg-Marquardt method with line-search [**31**]. This method is implemented in the built-in routine `lsqcurvefit.m` in MATLAB (The MathWorks, Inc.).

The asymptotic variance-covariance $\mathbf{AV}(\hat{\mathbf{\Theta}})$ of the least-squares estimate for the spatially explicit Model (3.2) was computed using a Brownian bridge error structure to model the stochastic temporal dependence of the cumulative number of outbreaks [**11, 12**]. The explicit formula used is

$$\mathbf{AV}(\hat{\mathbf{\Theta}}) = \sigma^{\mathbf{2}}\ \mathbf{B}(\mathbf{\Theta_0})\ \nabla_{\mathbf{\Theta}}\mathbf{C}(\mathbf{\Theta_0})^{\mathbf{T}}\ \mathbf{G}\ \nabla_{\mathbf{\Theta}}\mathbf{C}(\mathbf{\Theta_0})\ \mathbf{B}(\mathbf{\Theta_0}), \tag{3.7}$$

where $\mathbf{B}(\mathbf{\Theta_0}) = [\nabla_{\mathbf{\Theta}}\mathbf{C}(\mathbf{\Theta_0})^{\mathbf{T}}\ \nabla_{\mathbf{\Theta}}\mathbf{C}(\mathbf{\Theta_0})]^{-\mathbf{1}}$.

An estimate of $\mathbf{AV}(\hat{\mathbf{\Theta}})$ is

$$\hat{\sigma}^2\ \hat{\mathbf{B}}(\hat{\mathbf{\Theta}})\ \nabla_{\mathbf{\Theta}}\hat{\mathbf{C}}(\hat{\mathbf{\Theta}})^{\mathbf{T}}\ \mathbf{G}\ \nabla_{\mathbf{\Theta}}\hat{\mathbf{C}}(\hat{\mathbf{\Theta}})\ \hat{\mathbf{B}}(\hat{\mathbf{\Theta}}), \tag{3.8}$$

where $\hat{\mathbf{B}}(\hat{\mathbf{\Theta}}) = [\nabla_{\mathbf{\Theta}}\hat{\mathbf{C}}(\hat{\mathbf{\Theta}})^{\mathbf{T}}\ \nabla_{\mathbf{\Theta}}\hat{\mathbf{C}}(\hat{\mathbf{\Theta}})]^{-\mathbf{1}}$, $\hat{\sigma}^2 = \sum(y_i - C(t_i, \hat{\mathbf{\Theta}}))^2/(I_{1xn}\ \ \mathbf{G}\ \ I_{nx1})$ and $\nabla_{\Theta}\hat{\mathbf{C}}$ are numerical derivatives of $C(\hat{\mathbf{\Theta}})$. The error structure [**15**] was also modelled by a Brownian bridge ($\mathbf{G}$). Here $\mathbf{G}$ is an n x n matrix with entries $G_{i,j} = (1/n)\ \min(i,j) - (ij)/n^2$ where n is the total number of observations. $\mathbf{G}$ captures the higher variability in the cumulative number of outbreaks observed on the middle course of the epidemic as well as the smaller variability observed at the beginning and the end of the epidemic. Confidence intervals of 95% were computed using the asymptotic variance of our parameter estimates (diagonal elements of $\mathbf{AV}(\hat{\mathbf{\Theta}})$). The parameter estimates and their corresponding uncertainty are given in Table 1.

TABLE 1. Parameter definitions and estimates obtained from least-squares fitting of spatial epidemic model (3.2) to the cumulative number of infected farms in Region I [**11**].

Params.	Definition	Estim.	SD
β_0	Mean transm. rate within counties *before* mov. restrictions (1/days)	0.33	0.13
β	Mean transm. rate within counties *after* mov. restrictions (1/days)	0.10	0.03
$1/\alpha_0$	Mean time to detect infected farms *before* mov. restrictions (days)	7.14	1.02
$1/\alpha$	Mean time to detect infected farms *after* mov. restrictions (days)	7.14	1.02
$1/k$	Mean latent period (days)	3.57	0.64
q^*	Positive constant quantifying the extent of local spread (1/km)	1.03	0.10
$1/\nu$	Mean time to vaccination of susceptible farms (days)	4.00	1.44
$1/\mu$	Mean time to protection of vaccinated farms (days)	7.14	1.53

* Small values of q lead to widespread influence, while large values support local spread. Great mobility and frequent interactions among farms would lead to small values of q.

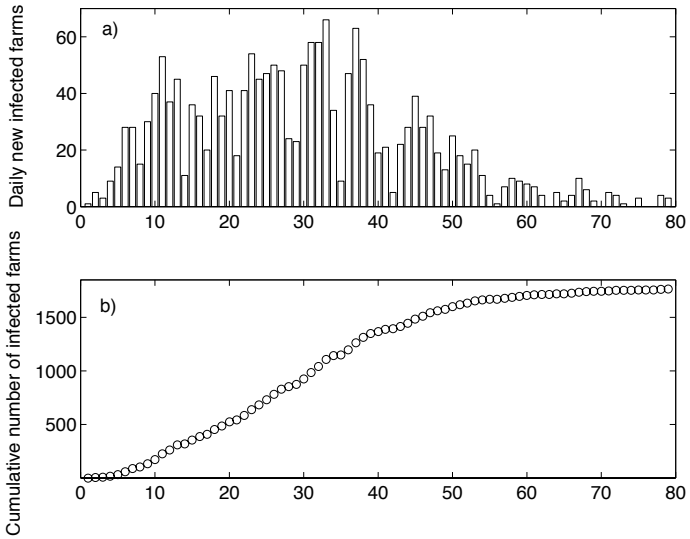

FIGURE 3. (a) Daily and (b) cumulative number of reported infected farms during the 2001 Foot and Mouth Disease epidemic in Uruguay. The epidemic reached its maximum of 66 outbreaks on day 33 (25 May 2001). By day 79 (10 July 2001) 1762 outbreaks had been reported. Data have been obtained from public records of the Uruguayan Ministry of Livestock, Agriculture, and Fisheries (MGAP), the Pan-american Health Organization, and the World Organization for Animal Health (OIE). The periodic dips in the data are due to low reporting rates on the weekends.

4. Results

The magnitude of the actual epidemic size utilized in this study for comparative purposes (observed cases) is shown in Table 2. Using a hypothetical "regular" vaccine, it is shown that the earliest vaccination campaign (initiated at epidemic day 5, the same day movement restrictions were imposed in the scenario under analysis) resulted in a reduction of total epidemic size equal to 48.5% (or 486 fewer cases than expected) relative to the baseline Uruguayan scenario where the actual time of start of post-outbreak vaccination was at epidemic day 12 with a "regular" vaccine with an estimated time to reach protective antibody titers of 7.1 days [**11**]. A 59.4% reduction was achieved when a "high-potency" vaccine was administered. Vaccinations initiated at epidemic days 8 and 12 were associated with reductions in epidemic size of 31.9% ("regular vaccine) or 51.7% ("high-potency" vaccine). In contrast, POV starting at day 15 yielded no reductions in epidemic size (Table 2). Compared to the "regular" vaccine, the "high- potency" vaccine was associated with additional reductions in epidemic size ranging between 21.2 and 29.1%. Therefore, in the scenario under analysis, the optimal date for initiating a post-outbreak vaccination was between the 5^{th} and the 8^{th} epidemic day. We found no interaction between the effect of the starting time of the mass vaccination program and the type of vaccine used. The size of the epidemic grows linearly

TABLE 2. Final epidemic size associated with POV initiated between epidemic days 5 and 15. Two vaccines are used: 1) a regular vaccine (RV) and 2) a high-potency vaccine (HP). Mass vaccinations (MV) are initiated at post-outbreak day (pod) 5, 8, 12, or 15.

actual epidemic size at 79 days	MV start pod	RV size	HPV size	effect due to RV	effect due to HPV	net effect due to HPV (HPV/RV)
1003	5	517	407	-486 (−48.5%)	-596 (−59.4%)	-110 (−21.2%)
	8	683	484	−380 (−31.90%)	−519 (51.7%)	−199 (−29.1%)
	12	984	711	−19 (−1.9%)	−292 (−29.1%)	−273 (−27.7%)
	15	1282	1004	+279 (+27.8%)	+1 (+0.1%)	−278 (−21.7%)

The number of cases observed in the actual epidemic (at 70 pod) in the region under analysis (Region I) was 1003. Negative values indicate reduced epidemic size, positive values indicate increased epidemic size.

with the starting time of the mass vaccination campaign. Visually, there is a small quadratic effect but it is not statistically significant (Figure 4).

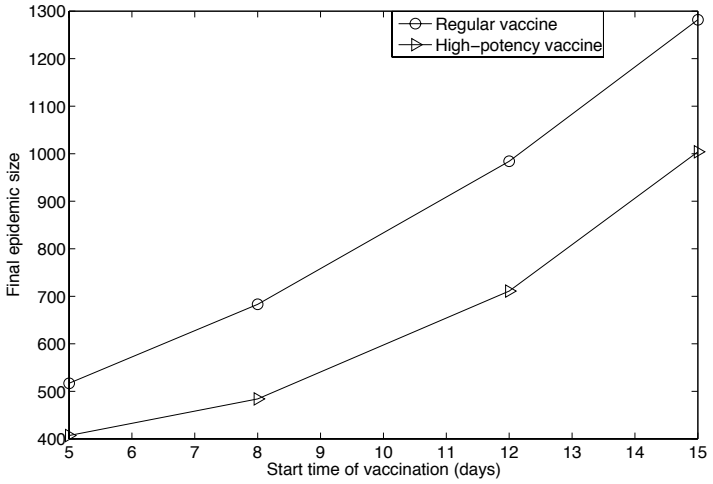

FIGURE 4. The final epidemic size as a function of the time of the start of the mass vaccination campaign and vaccine type. As can be seen from this figure, there is a small quadratic effect between the time of the start of the mass vaccination program (almost parallel curves) and the type of vaccine, but it is not statistically significant.

5. Discussion

Mathematical models have played an important role in the decision-making process in the control of FMD epidemics and its economic consequences [**21, 19, 29, 33, 8, 39, 34, 27, 5**]. During the 2001 FMD epidemic in Great Britain, different approaches were used including "moment closure" techniques [**19**] and stochastic models [**29, 33**]. Here, we used a spatially explicit deterministic model that takes into account the distance between counties in the transmission process (Figure 2), farm density within counties, and information on the timing of intervention strategies during the epidemic.

The evolution of epidemics is inherently a stochastic process. In large populations, the average epidemic described by a system of differential equations is close to the actual realization of the epidemic. In smaller populations, these differential equations models continue to describe the evolution of the average epidemic, while the actual realization can depart from its average. Our model attempts to describe simultaneously the average behavior of the epidemic within each of the 42 counties. Discrepancies between the actual epidemic data and the predicted average increase the residual sums of squares leading to larger standard deviations for the estimated parameters. This motivates the importance of attaching standard deviations to our estimates in our analysis.

The level of local and long-distance farm "interactions" naturally depend on farm "type." Data on farm heterogeneity (dairy, beef, etc) or farm composition (cattle, pigs, sheep) [**6, 44**] were not explicitly incorporated here but could be considered should appropriate data were to become available. Generally speaking, the estimates of the transmission rates (as previously defined) should be interpreted as mean transmission rates characteristic of the 2001 FMD epidemic in Uruguay. The explicit nature of the data and model assumptions suggest that these estimates are unlikely to be of value elsewhere. However, the modelling and estimation approach should be of use in similar situations.

In the scenario under analysis the "best" vaccination policy was the one that began at epidemic day 5 (time estimated to correspond to the second replication cycle, or epidemic days 4-6), and applied the high-potency vaccine. Because at least 3 additional days are deemed necessary to induce protective levels of antibodies against FMD virus (FMDV), the effects induced effects by this policy occurred during or after the third replication cycle of FMDV ($\sim$ epidemic days 9-12). That policy reduced the final epidemic size from 1003 cases to 407 cases (Table 2).
The second "best" policy was the one that induced effects during or after the fourth FMDV replication cycle (9^{th} epidemic day), which "saved" 51.7% of all cases (when a "high-potency" vaccine is used). The third (and last) policy inducing case reduction at levels approaching acceptability was the one generating protective antibodies after the fifth FMDV replication cycle (after the 15^{th} epidemic day). It reduced the total number of cases by 29.1%. In contrast, vaccinations inducing protective antibody titers at or after the 18^{th} epidemic day (after the sixth FMDV replication cycle) were not associated with reductions in epidemic size (Table 2).

In order to induce measurable reductions in the total epidemic size (in diseases where the time required to induce protective antibody titers is not greater than the replication cycle of the infective agent), POV has to be initiated not later than the time estimated to correspond to the fourth replication cycle of the infective agent. Even under the assumption of 100% efficacy (under experimental conditions) and

also under the assumption of 100% spatial coverage (no region with susceptible animals is left unvaccinated), post-outbreak vaccinations have a very narrow time window within which some significant reduction of epidemic size may occur (between the second and the fifth replication cycle of the infective agent). However, when regular vaccines are used, longer periods of time may be needed to induce protective titers of specific antibodies (i.e., at least equivalent to an additional [viral] replication cycle).

The brief timeframe available for implementing effective post-outbreak vaccinations, observed in this study, is compatible with previous reports. For example, Woolhouse et al. [**46**] has reported that post-outbreak (and even prophylactic) vaccinations have failed to prevent or have not been able to stop FMD epidemics in Saudi Arabia and Argentina. The basic reason is the fact that the combination of multiple replication cycles with even moderate reproductive numbers (the ratio of secondary cases per primary cases or R_0) result in very high numbers of infected premises within a brief time interval. For instance, an index case associated with a $R_0 = 4$ (e.g., 4 new cases are induced per primary case, in each replication cycle) results in 45 (256 cases) after the virus has replicated 5 times. Two-digit R_0's are rather common findings in early phases of FMD epidemics [**46**].

Because of these limitations, we concluded that post-outbreak vaccinations are unlikely to result in significant reductions of epidemic size. It is suggested that this approach, here evaluated in the context of FMD epidemics, may be adapted to other diseases (adjusting for the replication cycle of the specific infective agent) and can help decide whether the benefits involved in post-outbreak vaccinations (epidemic size reduction) outweigh their costs.

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